INVEGA® TRINZA™
paliperidone palmitate

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
See full prescribing information for complete boxed warning
- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death (5.1).**
- **INVEGA TRINZA is not approved for use in patients with dementia-related psychosis (5.1).**

NAME OF THE MEDICINAL PRODUCT
INVEGA TRINZA (350 mg paliperidone as 546 mg paliperidone palmitate) Prolonged-Release Suspension for Intramuscular Injection.
INVEGA TRINZA (525 mg paliperidone as 819 mg paliperidone palmitate) Prolonged-Release Suspension for Intramuscular Injection.

International Non-proprietary Name
Paliperidone palmitate 3-month injection.

DOSAGE FORMS AND STRENGTHS
INVEGA TRINZA contains 350, or 525 mg paliperidone (as 546, or 819 mg of paliperidone palmitate, respectively).
The chemical name is (±)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-9-yl hexadecanoate.
Prolonged-release suspension in prefilled syringes. The suspension is white to off-white.
For excipients, see *Section List of Excipients*.

CLINICAL INFORMATION
INDICATIONS
INVEGA TRINZA a 3-month injection, is indicated for the maintenance treatment of schizophrenia in adult patients who have been adequately treated with the 1-month paliperidone palmitate injectable product for at least four months.

DOSAGE AND ADMINISTRATION
INVEGA TRINZA is to be used only after the 1 month paliperidone palmitate injectable product has been established as adequate treatment for at least four months. In order to establish a consistent maintenance dose, it is recommended that the last two doses of the 1-month injection be the same dosage strength before starting INVEGA TRINZA.

Dosage
Initiate INVEGA TRINZA at the time when the next 1-month paliperidone palmitate dose was to be scheduled with a INVEGA TRINZA dose based on the previous 1-month injection dose as shown in Table 1. INVEGA TRINZA may be administered up to 7 days before or after the monthly time point of the next scheduled paliperidone palmitate 1-month dose.

Table 1. Conversion From the Last Paliperidone Palmitate 1-Month Injectable Product Dose To the Paliperidone Palmitate 3-Month Injectable Product (INVEGA TRINZA) Dose Using 3.5 as a Multiplier

If the last 1-month paliperidone palmitate injection dose is:	Initiate INVEGA TRINZA at the following dose:
100 mg	350 mg
150 mg	525 mg

Conversion from the 25 mg 1-month paliperidone palmitate injectable product was not studied.

Following the initial INVEGA TRINZA dose, INVEGA TRINZA should be administered every 3 months. If needed, dose adjustment can be made every 3 months in increments within the range of 175 mg to 525 mg based on individual patient tolerability and/or efficacy. Due to the long-acting nature of INVEGA TRINZA, the patient's response to an adjusted dose may not be apparent for several months (see *Pharmacokinetic Properties*)

Missed Doses
Dosing Window. Missing doses of INVEGA TRINZA should be avoided. However, on exceptional occasions, patients may be given the injection up to 2 weeks before or after the 3-month time point.

Missed Dose > 3½ Months up to 4 Months. If more than 3½ months (up to 4 months) have elapsed since the last injection of INVEGA TRINZA, the previously administered INVEGA TRINZA dose should be administered as soon as possible, then continue with the 3-month injections following this dose.

Missed Dose > 4 Months up to 9 Months. If more than 4 months (up to 9 months) have elapsed since the last injection of INVEGA TRINZA, do NOT administer the next dose of INVEGA TRINZA. Instead, use the re-initiation regimen shown in Table 2

Table 2. Re-initiation regimen after missing >4 months up to 9 months of INVEGA TRINZA

Last INVEGA TRINZA 3-Month Injectable Product Dose	Administer Paliperidone Palmitate 1-Month Injectable Product, two doses one week apart (into deltoid muscle)		Then administer INVEGA TRINZA 3-Month Injectable Product Dose (into deltoid[a] or gluteal muscle)
	Day 1	Day 8	1 month after Day 8
350 mg	100 mg	100 mg	350 mg
525 mg	100 mg	100 mg	525 mg

[a] See Instructions for Use for deltoid injection needle selection based on body weight.

Missed Dose > 9 Months. If more than 9 months have elapsed since the last injection of INVEGA TRINZA, re-initiate treatment with the 1-month paliperidone palmitate injectable product as described in the prescribing information for that product. INVEGA TRINZA can then be resumed after the patient has been adequately treated with the 1-month paliperidone palmitate injectable product for at least 4 months.

Administration Information
Parenteral drug products should be inspected visually for foreign matter and discoloration prior to administration. **Within 5 minutes prior to administration of INVEGA TRINZA to the patient, it is important to shake the syringe vigorously for at least 15 seconds to ensure a homogeneous suspension** (see *Instructions for Use and Handling and Disposal*).

INVEGA TRINZA is intended for intramuscular use only. Do not administer intravascularly or subcutaneously. Avoid inadvertent injection into a blood vessel. Each injection must be administered only by a health care professional. Administer the dose in a single injection; do not administer the dose in divided injections. Inject slowly, deep into the deltoid or gluteal muscle. Product is for single use in one patient only. Discard any residue.

INVEGA TRINZA must be administered using only the thin wall needles that are provided in the INVEGA TRINZA pack. Needles from the 1-month paliperidone palmitate injectable product pack or other commercially-available needles are not to be used when administering INVEGA TRINZA.

The recommended needle size for administration of INVEGA TRINZA into the deltoid muscle is determined by the patient's weight. For those ≥ 90 kg (≥ 200 lbs), the 1½-inch, 22 gauge thin wall needle is recommended. For those < 90 kg (< 200 lbs), the 1-inch, 22 gauge thin wall needle is recommended. Administer into the center of the deltoid muscle. Deltoid injections should be alternated between the two deltoid muscles.

The recommended needle size for administration of INVEGA TRINZA into the gluteal muscle regardless of body weight is the 1½-inch, 22 gauge thin wall needle. Administer into the upper-outer quadrant of the gluteal muscle. Gluteal injections should be alternated between the two gluteal muscles.

Since paliperidone is the active metabolite of risperidone, caution should be exercised when INVEGA TRINZA is coadministered with risperidone or with oral paliperidone for extended periods of time. Safety data involving concomitant use of INVEGA TRINZA with other antispychotics is limited.

Incomplete Administration. To avoid an incomplete administration of INVEGA TRINZA, ensure that the prefilled syringe is **shaken vigorously for at least 15 seconds within 5 minutes prior to administration to ensure a homogeneous suspension** (see *Instructions for Use and Handling and Disposal*). However, in the event of an incompletely administered dose, do not re inject the dose remaining in the syringe and do not administer another dose. Closely monitor and treat the patient appropriately until the next scheduled 3-month injection of INVEGA TRINZA.

Special populations
Pediatrics (less than 18 years of age)
Safety and effectiveness of INVEGA TRINZA in patients < 18 years of age have not been studied. Use in these patients is not recommended.

Elderly
In general, recommended dosing of INVEGA TRINZA for elderly patients with normal renal function is the same as for younger adult patients with normal renal function. As elderly patients may have reduced renal function, see Renal impairment below for dosing recommendations in patients with renal impairment.

Renal impairment
INVEGA TRINZA has not been systematically studied in patients with renal impairment (see *Pharmacokinetic Properties*). For patients with mild renal impairment (creatinine clearance ≥ 50 to < 80 mL/min), dose adjustment is done when initiating treatment with the 1-month paliperidone palmitate injectable product; no dose adjustment of INVEGA TRINZA is required.

Transition to INVEGA TRINZA is with a dose in a 3.5 to 1 ratio to the previous stabilized 1-month paliperidone palmitate injectable product as described in *Dosage* above. The maximum recommended dose of INVEGA TRINZA in patients with mild renal impairment is 350 mg.

INVEGA TRINZA is not recommended in patients with moderate or severe renal impairment (creatinine clearance < 50 ml/min).

Hepatic impairment
INVEGA TRINZA has not been studied in patients with hepatic impairment. Based on a study with oral paliperidone, no dose adjustment is required in patients with mild or moderate hepatic impairment. Paliperidone has not been studied in patients with severe hepatic impairment. (See *Pharmacokinetic Properties).*

Other populations
No dose adjustment for INVEGA TRINZA is recommended based on gender, race, or smoking status. (For pregnant women and nursing mothers, see *Pregnancy and Breast-feeding*.)

Switching from other antipsychotic agents
INVEGA TRINZA is to be used only after the patient has been adequately treated with the 1 month paliperidone palmitate injectable product for at least 4 months (see *Indications* and *Dosage and Administration*).
If INVEGA TRINZA is discontinued, its prolonged-release characteristics must be considered. As recommended with other antipsychotic medications, the need for continuing existing extrapyramidal symptoms (EPS) medication should be re-evaluated periodically.

Switching from INVEGA TRINZA *to the 1-Month Paliperidone Palmitate Injectable Product*
For switching from INVEGA TRINZA to the 1-month paliperidone palmitate injectable product, the 1-month paliperidone palmitate injectable product should be administered at the time the next INVEGA TRINZA dose was to be administered using the equivalent 3.5-fold lower dose as shown in Table 3. The 1-month paliperidone palmitate injectable product should then continue dosed at monthly intervals.

Table 3. Conversion From the Last Paliperidone Palmitate 3-Month Injectable Product (INVEGA TRINZA) Dose To the Paliperidone Palmitate 1-Month Injectable Product Dose Using 3.5 as a conversion factor

If the last INVEGA TRINZA dose is:	Administer 1-Month Paliperidone Palmitate at the following dose:
350 mg	100 mg
525 mg	150 mg

The initiation dosing as described in the prescribing information for the 1-month paliperidone palmitate injectable product is not required.

Switching from INVEGA TRINZA to Oral Paliperidone Extended-Release Tablets
For switching from INVEGA TRINZA to oral paliperidone extended-release tablets, the daily dosing of the paliperidone extended-release tablets should be started 3 months after the last INVEGA TRINZA dose and transitioned over the next several months following the last INVEGA TRINZA dose as described in Table 4. Table 4 provides dose conversion regimens to allow patients previously stabilized on different doses of INVEGA TRINZA to attain similar paliperidone exposure with once daily paliperidone extended-release tablets.

Table 4. INVEGA TRINZA doses and once-daily paliperidone extended-release conversion regimens needed to attain similar paliperidone exposures*

	Weeks since last INVEGA TRINZA dose		
	≥ 3 months to ≤ 18 weeks	> 18 weeks to ≤ 24 weeks	> 24 weeks
Last INVEGA TRINZA Dose	**Daily dose of oral paliperidone extended-release tablets**		
350 mg	3 mg	6 mg	9 mg
525 mg	6 mg	9 mg	12 mg

*Doses of oral paliperidone extended-release tablets should be individualized taking into consideration the reason for switching, response to previous paliperidone treatment, severity of psychotic symptoms, and/or tolerability

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
Pharmacotherapeutic group: Other antipsychotics, ATC code: N05AX13.

Mechanism of Action
Paliperidone palmitate, the active ingredient in INVEGA TRINZA, is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives (atypical neuroleptic antipsychotic). INVEGA TRINZA contains a racemic mixture of (+)- and (-)-paliperidone.

Paliperidone palmitate is hydrolyzed to paliperidone (see *Non-clinical Information*). Paliperidone is a centrally active dopamine D2 antagonist with predominant serotonergic 5-HT_{2A} antagonistic activity. Paliperidone is also active as an

antagonist at α1 and β2 adrenergic receptors and H1 histaminergic receptors. Paliperidone has no affinity for cholinergic muscarinic or α1- and β2- adrenergic receptors. The pharmacological activity of the (+)– and (-)-paliperidone enantiomers is qualitatively and quantitatively similar.

The mechanism of action of paliperidone, as with other drugs having efficacy in schizophrenia, is unknown. It has been proposed that the therapeutic activity of paliperidone in schizophrenia is mediated through a combination of dopamine Type 2 (D2) and serotonin Type 2 ($5HT_{2A}$) receptor antagonism. Antagonism at receptors other than D2 and 5HT2A may explain some of the other effects of paliperidone.

Effect on QT/QTc interval and cardiac electrophysiology
The effects of paliperidone on the QT interval were evaluated in a double-blind, active controlled (moxifloxacin 400 mg single dose), multicenter Thorough QT study with oral paliperidone in adults with schizophrenia and schizoaffective disorder, and in four fixed-dose efficacy studies and one maintenance study of the 1-month paliperidone palmitate injectable product.

In the Thorough QT study (n = 141), the 8 mg dose of immediate-release oral paliperidone (n=50) showed a mean placebo-subtracted increase from baseline in QTcLD (QT interval corrected for heart rate using the population specified linear derived method) of 12.3 msec (90% CI: 8.9; 15.6) on day 8 at 1.5 hours post-dose. The mean steady-state peak plasma concentration for this 8 mg dose of paliperidone immediate release ($C_{max\ ss}$ = 113 ng/mL) was approximately 2 fold the exposure with the maximum recommended 525 mg dose of INVEGA TRINZA administered in the deltoid muscle (predicted median $C_{max\ ss}$ = 56 ng/mL). In this same study, a 4 mg dose of the immediate-release oral formulation of paliperidone, for which $C_{max\ ss}$ = 35 ng/mL, showed an increased placebo-subtracted QTcLD of 6.8 msec (90% CI: 3.6; 10.1) on day 2 at 1.5 hours post-dose.

In the four fixed-dose efficacy studies of the 1-month paliperidone palmitate injectable product, no subject had a change in QTcLD exceeding 60 msec and no subject had a QTcLD value of > 500 msec at any time point. In the maintenance study, no subject had a QTcLD change > 60 msec, and one subject had a QTcLD value of 507 msec (Bazett's QT corrected interval [QTcB] value of 483 msec); this latter subject also had a heart rate of 45 beats per minute.

In the long-term relapse prevention trial of INVEGA TRINZA in subjects with schizophrenia, an increase in QTcLD exceeding 60 msec was observed in 1 subject (< 1%) in the open-label phase, no subject had an increase in QTcLD exceeding 60 msec after treatment with INVEGA TRINZA in the double-blind phase, and no subject had a QTcLD value of > 480 msec at any point in the study.

Clinical efficacy
The efficacy of INVEGA TRINZA for the treatment of schizophrenia in subjects who have been adequately treated for at least 4 months with the 1-month paliperidone palmitate injectable product was evaluated in a long-term double-blind, placebo-controlled relapse prevention/randomized withdrawal study and in a long-term double-blind, active-controlled noninferiority study.

Relapse prevention / randomized withdrawal study
Adult subjects who met DSM-IV-TR criteria for schizophrenia could enter the study with acute symptoms (if previously treated with oral antipsychotics) or be clinically stable (if treated with long-acting injectable antipsychotics [LAI]). All subjects who previously received oral antipsychotics received the paliperidone palmitate 1-month initiation regimen (deltoid injections of 234 mg and 156 mg one week apart), while those subjects switching from LAI medication were treated with the 1-month paliperidone palmitate injectable product in place of the next scheduled injection. Specifically:

- For subjects entering the study who were already being treated with the 1-month paliperidone palmitate injectable product, their dosing remained unchanged. Subjects who were currently receiving the 39 mg dose of 1-month paliperidone palmitate were not eligible to enroll in the study.
- Subjects entering the study who were being treated with 25 mg, 37.5 mg, or 50 mg of RISPERDAL® CONSTA® (risperidone long-acting injection) were switched to 78 mg, 117 mg, or 156 mg, respectively, of the 1-month paliperidone palmitate administered in the deltoid muscle.
- Subjects entering the study who were being treated with any other LAI product were switched to 234 mg of the 1-month paliperidone palmitate administered in the deltoid muscle.

This study consisted of the following three treatment periods:

- A 17-week flexible-dose open-label period with the 1-month paliperidone palmitate (first part of a 29-week open-label stabilization phase). A total of 506 subjects entered this phase of the study. Dosing of the 1-month paliperidone palmitate was individualized based on symptom response, tolerability, and previous medication history. Specifically, the dose could be adjusted at the week 5 and 9 injections and the injection site could be deltoid or gluteal. The week 13 dose had to be the same as the week 9 dose. Subjects had to be clinically stable at the end of this period before receiving INVEGA TRINZA at the week 17 visit. Clinical stability was defined as achieving a PANSS total score < 70 at week 17.
- A 12-week open-label treatment period with INVEGA TRINZA (second part of a 29-week open-label stabilization phase). A total of 379 subjects received a single-dose of INVEGA TRINZA which was a 3.5 multiple of the last dose of the 1-month paliperidone palmitate. Subjects had to remain clinically stable before entry into the next period (double-blind). Clinical stability was defined as achieving a PANSS total score < 70 and scores of ≤ 4 for PANSS items P1, P2, P3, P6, P7, G8, and G14 at the end of this 12-week period (week 29 of the study).
- A variable length double-blind treatment period. In this period, 305 stabilized subjects were randomized 1:1 to continue treatment with INVEGA TRINZA or placebo until relapse, early withdrawal, or the end of study. Subjects were randomized

to the same dose of INVEGA TRINZA they received during the open-label phase (i.e., 273 mg, 410 mg, 546 mg, or 819 mg) or to placebo administered every 12 weeks. The numbers (%) of subjects entering double-blind on each of the dose levels were 6 (4%) for 175 mg, 15 (9%) for 263 mg, 78 (49%) for 350 mg, and 61 (38%) for 525 mg.

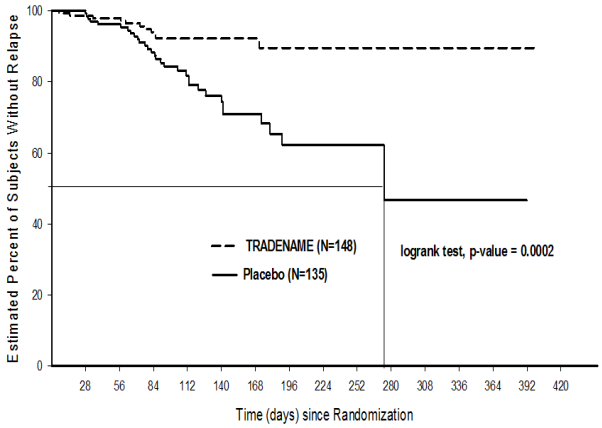
The primary efficacy variable was time to first relapse. Relapse was pre-defined as emergence of one or more of the following: psychiatric hospitalization, ≥ 25% increase (if the baseline score was > 40) or a 10-point increase (if the baseline score was ≤ 40) in total PANSS score on two consecutive assessments, deliberate self-injury, violent behavior, suicidal/homicidal ideation, or a score of ≥ 5 (if the maximum baseline score was ≤ 3) or ≥ 6 (if the maximum baseline score was 4) on two consecutive assessments of the individual PANSS items P1 (Delusions), P2 (Conceptual disorganization), P3 (Hallucinatory behavior), P6 (Suspiciousness/persecution), P7 (Hostility), or G8 (Uncooperativeness).

A pre-planned interim analysis showed a statistically significantly longer time to relapse in subjects treated with INVEGA TRINZA compared to placebo, and the study was stopped early because efficacy was demonstrated. The most common reason for relapse observed across both treatment groups was increase in the PANSS total score value, followed by psychiatric hospitalization.

The mean (SD) duration of exposure during the double-blind phase was 150 (79) days in the placebo group and 175 (90) days in the INVEGA TRINZA group. Twenty-three percent (23%) of subjects in the placebo group and 7.4% of subjects in the INVEGA TRINZA group experienced a relapse event. The hazard ratio for relapse (placebo/ INVEGA TRINZA) was 3.45 (95% CI: 1.73, 6.88) indicating a 71% decrease in relapse risk with INVEGA TRINZA. There was a significant difference (p-value <0.001) between the treatment groups in favor of INVEGA TRINZA. A Kaplan-Meier plot of time to relapse by treatment group is shown in Figure 1. The median time to relapse (the time at which the cumulative survival function equals 0.5, or 50%) for subjects in the placebo group (274 days) was significantly shorter than for the INVEGA TRINZA group (which could not be estimated as less than 15% of the remaining patients at any time during the trial experienced a relapse).

An examination of population subgroups did not reveal any clinically significant differences in responsiveness on the basis of gender, age, or race.

Figure 1: Kaplan-Meier Plot of Time to Relapsea – Interim Analysis

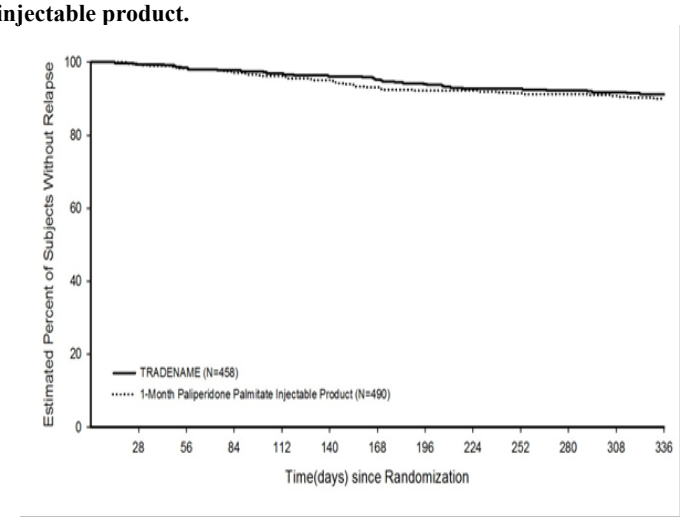


[a]Also depicted is the median time to relapse of the placebo group (274 days), which is an estimation of the average time it took for 50% of the trial population to relapse after INVEGA TRINZA was discontinued.

Noninferiority study
In the noninferiority study, 1429 acutely ill subjects (baseline mean PANSS total score: 85.7) were enrolled into the open-label phase and treated with the 1 month paliperidone palmitate injectable product for 17 weeks. The dose could be adjusted (i.e., 50 mg, 75 mg, 100 mg, or 150 mg) at the week 5 and 9 injections and the injection site could be deltoid or gluteal. For subjects that met randomization criteria at weeks 14 and 17, 1016 were randomized in a 1:1 ratio to continue on monthly injections of the 1-month paliperidone palmitate injectable product or to switch to INVEGA TRINZA with a 3.5 multiple of the week 9 and 13 dose of the 1-month paliperidone palmitate injectable product for 48 weeks. Subjects received INVEGA TRINZA once every 3 months and received placebo injectable medication for the other months to maintain the blind.

The primary efficacy endpoint of the study was the percentage of subjects who had not relapsed at the end of the 48-week double-blind phase based on the Kaplan-Meier 48-week estimate (INVEGA TRINZA: 91.2%, 1-month paliperidone palmitate injectable product: 90.0%). The mean (SD) duration of exposure during the double-blind phase was 295 (88) days in the INVEGA TRINZA group and 287 (96) days in the 1-month paliperidone palmitate injectable product group. The median time to relapse in either group could not be estimated due to low percentage of subjects with relapse. The difference (95% CI) between the treatment groups was 1.2% (-2.7%, 5.1%), meeting the pre-specified noninferiority criterion based on a margin of 15%. Thus, the INVEGA TRINZA treatment group was noninferior to the 1-month paliperidone palmitate injectable product. Improvements in functioning, as measured by the Personal and Social Performance scale (PSP), which was observed during the open-label stabilization phase were maintained during the double-blind phase for both treatment groups.

Figure 2: Kaplan-Meier Plot of time to relapse comparing INVEGA TRINZA and 1-month paliperidone palmitate injectable product.



The efficacy results were consistent across population subgroups (gender, age, and race) in both studies.

Pharmacokinetic Properties

Absorption and Distribution

Due to its extremely low water soluility, the 3-month formulation of paliperidone palmitate dissolves slowly after intramuscular injection before being hydrolyzed to paliperidone and absorbed into the systemic circulation. The release of the drug starts as early as day 1 and lasts for as long as 18 months.

The data presented in this paragraph are based on a population pharmacokinetic analysis. Following a single intramuscular dose of INVEGA TRINZA, the plasma concentrations of paliperidone gradually rise to reach maximum plasma concentrations at a median Tmax of 30 33 days. Following intramuscular injection of INVEGA TRINZA at doses of 175-525 mg in the deltoid muscle, on average, an 11-12% higher Cmax was observed compared with injection in the gluteal muscle. The release profile and dosing regimen of INVEGA TRINZA results in sustained therapeutic concentrations. The total exposure of paliperidone following INVEGA TRINZA administration was dose-proportional over a 175-525 mg dose range, and approximately dose-proportional for Cmax. The mean steady-state peak:trough ratio for a INVEGA TRINZA dose was 1.6 following gluteal administration and 1.7 following deltoid administration. Following administration of INVEGA TRINZA, the apparent volume of distribution of paliperidone is 1960 L.

The plasma protein binding of racemic paliperidone is 74%.
Following administration of INVEGA TRINZA, the (+) and (-) enantiomers of paliperidone interconvert, reaching an AUC (+) to (-) ratio of approximately 1.7-1.8.

Metabolism and Excretion

In a study with oral immediate-release ^{14}C-paliperidone, one week following administration of a single oral dose of 1 mg immediate-release ^{14}C paliperidone, 59% of the dose was excreted unchanged into urine, indicating that paliperidone is not extensively metabolized in the liver. Approximately 80% of the administered radioactivity was recovered in urine and 11% in the feces. Four metabolic pathways have been identified in vivo, none of which accounted for more than 10% of the dose: dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission. Although *in vitro* studies suggested a role for CYP2D6 and CYP3A4 in the metabolism of paliperidone, there is no evidence *in vivo* that these isozymes play a significant role in the metabolism of paliperidone. Population pharmacokinetics analyses indicated no discernible difference on the apparent clearance of paliperidone after administration of oral paliperidone between extensive metabolizers and poor metabolizers of CYP2D6 substrates. *In vitro* studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of medicines metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5.

In vitro studies have shown that paliperidone is a P-gp substrate and a weak inhibitor of P-gp at high concentrations. No *in vivo* data are available and the clinical relevance is unknown.

Based on population pharmacokinetic analysis, the median apparent half-life of paliperidone following INVEGA TRINZA administration over the dose range of 175-525 mg ranged from 84 95 days following deltoid injections and 118-139 days following gluteal injections.

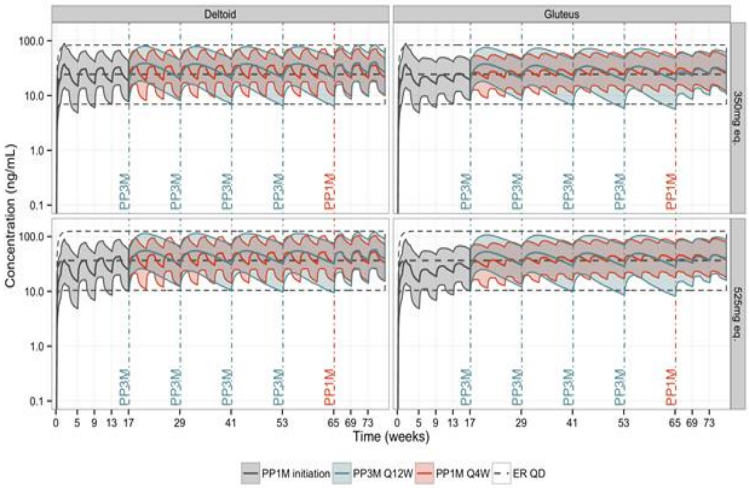
Long-acting 3-month paliperidone palmitate injection versus other paliperidone formulations

The concentration of paliperidone remaining in the circulation 18 months after dosing of 525 mg INVEGA TRINZA is stopped is estimated to be 3% (following deltoid injection) or 7% (following gluteal injection) of the average steady-state levels.

INVEGA TRINZA is designed to deliver paliperidone over a 3-month period, while 1-month paliperidone palmitate injection is administered on a monthly basis. Simulations show that INVEGA TRINZA, when administered at doses that are 3.5 fold higher than the corresponding dose of 1-month paliperidone palmitate injection, produces paliperidone exposures similar to those obtained with corresponding monthly doses of 1-month paliperidone palmitate injection and corresponding once daily doses of paliperidone extended-release tablets; and that exposure range for INVEGA TRINZA is encompassed within the exposure range for the approved dose strengths of paliperidone extended-release tablets.

Figure 3 presents the population predicted median pharmacokinetic profiles for paliperidone following INVEGA TRINZA administration using the 350 mg and 525 mg doses compared to the administration of monthly injections of 100 mg and 150 mg 1-month paliperidone palmitate injection and to oral extended-release tablet administration (8 mg or 12 mg). Treatment with 1 month paliperidone palmitate injection for at least 4 months prior to initiating treatment with INVEGA TRINZA resulted in maintenance of steady-state paliperidone plasma exposures.

Figure 3. Predicted paliperidone plasma concentrations versus time for INVEGA TRINZA (PP3M) 350 mg and 525 mg dose groups compared to the monthly dosing of 1-month paliperidone palmitate injection (PP1M) 100 mg and 150 mg. The dashed lines represent the predicted paliperidone concentrations following treatment with 8 mg and 12 mg oral paliperidone extended-release tablets.



The between-subject variability for paliperidone pharmacokinetics following delivery from INVEGA TRINZA is similar to the variability for paliperidone extended-release tablets. Because of the difference in median pharmacokinetic profiles among the three paliperidone formulations, caution should be exercised when making a direct comparison of their pharmacokinetic behavior in a given patient.

Special Populations
Elderly (65 years of age and older)
No dosage adjustment is recommended based on age alone. However, dose adjustment may be required because of age-related decreases in creatinine clearance (see *Renal impairment below and Dosage and Administration).*

Renal impairment
INVEGA TRINZA has not been systematically studied in patients with renal impairment. The disposition of a single oral dose of a paliperidone 3 mg extended-release tablet was studied in subjects with varying degrees of renal function. Elimination of paliperidone decreased with decreasing estimated creatinine clearance. Total clearance of paliperidone was reduced in subjects with impaired renal function by 32% on average in mild (CrCl = 50 to < 80 mL/min), 64% in moderate (CrCl = 30 to < 50 mL/min), and 71% in severe (CrCl = 10 to < 30 mL/min) renal impairment, corresponding to an average increase in exposure (AUC_{inf}) of 1.5, 2.6, and 4.8 fold, respectively, compared to healthy subjects. Based on a limited number of observations with INVEGA TRINZA in subjects with mild renal impairment and pharmacokinetic simulations, the initiation and maintenance dose of 1-month paliperidone palmitate injection should be reduced in patients with mild renal impairment. Subjects can be transitioned over to INVEGA TRINZA using the corresponding 3.5-multiple dose for mild renal impaired subjects. No additional dose reduction upon starting INVEGA TRINZA is necessary. (see *Dosage and Administration)*

Hepatic impairment
Paliperidone is not extensively metabolized in the liver. Although INVEGA TRINZA was not studied in patients with hepatic impairment, no dose adjustment is required in patients with mild or moderate hepatic impairment. In a study with oral paliperidone in subjects with moderate hepatic impairment (Child-Pugh class B), the plasma concentrations of free paliperidone were similar to those of healthy subjects. Paliperidone has not been studied in patients with severe hepatic impairment.

Race.

Population pharmacokinetics analysis of data from studies with oral paliperidone revealed no evidence of race-related differences in the pharmacokinetics of paliperidone following INVEGA TRINZA administration.

Gender.
No clinically significant differences were observed between men and women.

Smoking Status.
Based on *in vitro* studies utilizing human liver enzymes, paliperidone is not a substrate for CYP1A2; smoking should, therefore, not have an effect on the pharmacokinetics of paliperidone. Consistent with these *in vitro* results, population pharmacokinetic evaluation has not revealed any differences between smokers and non-smokers.

Body Mass Index (BMI)/Body Weight
No dose adjustment is needed based on BMI. Lower C_{max} was observed in overweight and obese subjects. At apparent steady-state with INVEGA TRINZA, the trough concentrations were similar among normal, overweight, and obese subjects.

Non Clinical Information
Toxicology
As with other drugs that antagonize dopamine D_2 receptors, intramuscularly-injected paliperidone palmitate, as well as orally-dosed paliperidone, elevated serum prolactin levels in repeat-dose toxicity studies.

In a 7-week juvenile toxicity study in rats with oral doses of paliperidone of 0.16, 0.63, and 2.5 mg/kg/day, which are 0.12, 0.5, and 1.8 times the maximum recommended human oral dose of 12 mg/day for adolescents on a mg/m2 basis, no effects on growth, sexual maturation, and reproductive performance were observed. Oral doses up to 2.5 mg/kg/day did not impair neurobehavioral development in males and females, except for an effect on learning and memory in female rats treated at 2.5 mg/kg/day. This effect was not observed after discontinuation of treatment.

In a 40-week study in juvenile dogs treated with oral risperidone (which is extensively converted to paliperidone) at doses of 0.31, 1.25, and 5 mg/kg/day, sexual maturation was not adversely affected at 0.31 and 1.25 mg/kg/day. Long bone growth was not affected at 0.31 mg/kg/day; effects were observed at 1.25 and 5 mg/kg/day.

Carcinogenicity
The carcinogenic potential of intramuscularly injected paliperidone palmitate was assessed in rats. There was a statistically significant increase in mammary gland adenocarcinomas in female rats at 10, 30 and 60 mg /kg/month, which are 0.2, 0.6, and 1.1 times the maximum recommended INVEGA TRINZA human dose of 525 mg on a mg/m2 body surface area basis. Male rats showed a statistically significant increase in mammary gland adenomas and carcinomas at 30 and 60 mg/kg/month which is 1.3 and 2.5 times the maximum recommended human 525 mg dose of INVEGA TRINZA on a mg/m^2 basis.

The carcinogenic potential of oral paliperidone, an active metabolite of risperidone, was assessed based on studies with risperidone conducted in mice and rats. Risperidone was administered at doses up to 10 mg/kg/day for 18 months to mice and for 25 months to rats. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. An increase in mammary, pituitary, and endocrine pancreas tumors has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be mediated by prolonged dopamine D_2 antagonism. The relevance of these tumor findings in rodents in terms of human risk is unknown.

Mutagenicity
No evidence of mutagenic potential for paliperidone was found in the Ames reverse mutation test, the mouse lymphoma assay, or the rat micronucleus test. Paliperidone palmitate showed no genotoxic properties in the Ames reverse mutation test or the mouse lymphoma assay.

Fertility
Although oral paliperidone treatment resulted in prolactin- and CNS-mediated effects, the fertility of male and female rats was not affected. At a maternally toxic dose, female rats showed a slightly lower number of live embryos.

WARNINGS AND PRECAUTIONS
Neuroleptic Malignant Syndrome
Neuroleptic Malignant Syndrome (NMS), characterized by hyperthermia, muscle rigidity, autonomic instability, altered consciousness, and elevated serum creatine phosphokinase levels has been reported to occur with antipsychotic drugs, including paliperidone. Additional clinical signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. If a patient develops signs or symptoms indicative of NMS, all antipsychotic drugs, including INVEGA TRINZA, should be discontinued. Consideration should be given to the long-acting nature of INVEGA TRINZA.
If a patient appears to require antipsychotic drug treatment after recovery from NMS, reintroduction of drug therapy should be closely monitored, since recurrences of NMS have been reported.
If NMS has occurred with any paliperidone product, INVEGA TRINZA should not be used.

Tardive Dyskinesia/extrapyramidal symptoms
Drugs with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia characterized by rhythmical, involuntary movements, predominantly of the tongue and/or face. If signs and symptoms of

tardive dyskinesia appear, the discontinuation of all antipsychotic drugs, including INVEGA TRINZA, should be considered. Consideration should be given to the long-acting nature of INVEGA TRINZA.

Extrapyramidal symptoms and psychostimulants
Caution is warranted in patients receiving both psychostimulants (e.g. methylphenidate) and paliperidone concomitantly, as extrapyramidal symptoms could emerge when adjusting one or both medications.

QT Interval
Paliperidone causes a modest increase in the corrected QT (QTc) interval. The use of paliperidone should be avoided in combination with other drugs that are known to prolong QTc including Class 1A (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (e.g., chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval. Paliperidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias.
Certain circumstances may increase the risk of the occurrence of Torsades de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval.
As with other antipsychotics, caution should be exercised when INVEGA TRINZA is prescribed in patients with a history of cardiac arrhythmias, in patients with congenital long QT syndrome, and in concomitant use with drugs known to prolong the QT interval. (see *Pharmacodynamic Properties: Effect on QT/QTc interval and cardiac electrophysiology*).
If clinically significant QT prolongation has occurred with any paliperidone product, INVEGA TRINZA should not be used.

Hypersensitivity reactions
Anaphylactic reactions in patients who have previously tolerated oral risperidone or oral paliperidone have been very rarely reported during post marketing experience with the 1-month paliperidone palmitate injectable product (see *Dosage and Administration* and *Adverse Reactions*).
If hypersensitivity reactions occur, discontinue use of INVEGA TRINZA; initiate general supportive measures as clinically appropriate and monitor the patient until signs and symptoms resolve. (See *Contraindications* and *Adverse Reactions*.)

Hyperglycemia and diabetes mellitus
Hyperglycemia, diabetes mellitus, and exacerbation of pre existing diabetes have been reported during treatment with antipsychotic drugs. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. Any patient treated with atypical antipsychotics, including INVEGA TRINZA should be monitored for symptoms of hyperglycemia and diabetes mellitus. (See also *Adverse Reactions*).

Weight gain
Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Orthostatic Hypotension
Paliperidone may induce orthostatic hypotension in some patients based on its alpha-blocking activity. INVEGA TRINZA should be used with caution in patients with known cardiovascular disease (e.g., heart failure, myocardial infarction or ischemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration, hypovolemia, and treatment with antihypertensive medications).

Seizures
As with other antipsychotic drugs, INVEGA TRINZA should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.
INVEGA TRINZA is not approved for the treatment of patients with dementia-related psychosis (see Boxed Warning).
Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis.
In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. No studies have been conducted with oral paliperidone, the 1-month paliperidone palmitate extended-release injectable suspension, or INVEGA TRINZA® in elderly patients with dementia. These medications are not approved for the treatment of patients with dementia-related psychosis (see Boxed Warning).

Overall Mortality
In a meta-analysis of 17 controlled clinical trials, elderly patients with dementia treated with other atypical antipsychotic drugs, including risperidone, aripiprazole, olanzapine, and quetiapine, had an increased risk of mortality compared to placebo. Among those treated with risperidone, the mortality was 4% compared with 3.1% for placebo.

Cerebrovascular Adverse Events
In placebo-controlled trials in elderly patients with dementia treated with some atypical antipsychotic drugs, including risperidone, aripiprazole, and olanzapine, there was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischemic attacks) including fatalities, compared to placebo.

Leukopenia, neutropenia, and agranulocytosis
Events of leukopenia, neutropenia, and agranulocytosis have been reported with antipsychotic agents, including paliperidone. Agranulocytosis has been reported very rarely (< 1/10000 patients) during postmarketing surveillance.
Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia should be monitored during the first few months of therapy and discontinuation of INVEGA TRINZA should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.
Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1 X 109/L) should discontinue INVEGA TRINZA and have their WBC followed until recovery.
Consideration should be given to the long-acting nature of INVEGA TRINZA.

Venous thromboembolism
Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with INVEGA TRINZA and preventive measures undertaken.

Parkinson's Disease and Dementia with Lewy Bodies
Physicians should weigh the risks versus the benefits when prescribing antipsychotic drugs, including INVEGA TRINZA, to patients with Parkinson's Disease or Dementia with Lewy Bodies (DLB) since both groups may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medications. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Priapism
Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Priapism has been reported with paliperidone during postmarketing surveillance (see *Adverse Reactions*).

Body Temperature Regulation
Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing INVEGA TRINZA to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Antiemetic Effect
An antiemetic effect was observed in preclinical studies with paliperidone. This effect, if it occurs in humans, may mask the signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Administration
Care must be taken to avoid inadvertent injection of INVEGA TRINZA into a blood vessel.

Intraoperative floppy iris syndrome
Intraoperative floppy iris syndrome (IFIS) has been observed during cataract surgery in patients treated with medicines with alpha1a-adrenergic antagonist effect, such as INVEGA TRINZA (see *Adverse Reactions*).
IFIS may increase the risk of eye complications during and after the operation. Current or past use of medicines with alpha1a-adrenergic antagonist effect should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping alpha1 blocking therapy prior to cataract surgery has not been established and must be weighed against the risk of stopping the antipsychotic therapy.

CONTRAINDICATIONS
INVEGA TRINZA is contraindicated in patients with a known hypersensitivity to paliperidone or to any of the components in the formulation. Since paliperdone is an active metabolite of risperidone, INVEGA TRINZA is contraindicated in patients with a known hypersensitivity to risperidone.

ADVERSE REACTIONS

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of paliperidone palmitate based on the comprehensive assessment of the available adverse event information. A causal relationship with paliperidone palmitate cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical Trial Data

The data described in this section include data from 3 clinical trials. One was a long-term relapse-prevention/randomized withdrawal trial, in which 506 subjects with schizophrenia received the 1-month paliperidone palmitate injectable product during the open-label phase, of which 379 subjects continued to receive a single injection of INVEGA TRINZA during the open-label phase, and 160 subjects were subsequently randomized to receive at least one dose of INVEGA TRINZA and 145 subjects received placebo during the double-blind placebo-controlled phase. The mean (Standard Deviation [SD]) duration of exposure during the double-blind phase was 150 (79) days in the placebo group and 175 (90) days in the INVEGA TRINZA group.

The second trial was a long-term double-blind, active-controlled noninferiority study, in which 1429 acutely ill subjects were enrolled into the open-label phase and treated with the 1 month paliperidone palmitate injectable product. Subjects who met the randomization criteria were randomized in a 1:1 ratio to continue on monthly injections of the 1-month paliperidone palmitate injectable product (n=512) or to switch to INVEGA TRINZA (n=504) for 48 weeks. The mean (SD) duration of exposure during the double-blind phase was 295 (88) days in the INVEGA TRINZA group and 287 (96) days in the 1-month paliperidone palmitate injectable product group.

The third trial was a Phase 1 study, in which 308 subjects with schizophrenia or schizoaffective disorder received a single injection of INVEGA TRINZA concomitantly with other oral antipsychotics.

The majority of adverse reactions were mild to moderate in severity.

Adverse reactions reported in the long-term relapse-prevention trial are shown in Table 5.

Table 5. Incidences of Adverse Reactions Identified for INVEGA TRINZA Summarized by Grouped Term for the Open-Label and Double-Blind Phases of a Long-Term Relapse Prevention Trial in Subjects with Schizophrenia

	--- Open Label-----	---------- Double Blind ----------	
	Paliperidone Palmitate[a]	**Placebo**	**INVEGA TRINZA**
System Organ Class	**(N=506)**	**(N=145)**	**(N=160)**
Adverse Reaction[b]	**n (%)[c]**	**n (%)[c]**	**n (%)[c]**
Infections and infestations			
Upper respiratory tract infection	26 (5.1)	6 (4.1)	16 (10.0)
Urinary tract infection	2 (0.4)	2 (1.4)	5 (3.1)
Metabolism and nutrition disorders			
Hyperglycemia	0	7 (4.8)	3 (1.9)
Hyperinsulinemia	0	1 (0.7)	1 (0.6)
Weight increased	52 (10.3)	5 (3.4)	14 (8.8)
Psychiatric disorders			
Anxiety	44 (8.7)	16 (11.0)	13 (8.1)
Nervous system disorders			
Akathisia	23 (4.5)	3 (2.1)	8 (5.0)
Dyskinesia	1 (0.2)	2 (1.4)	1 (0.6)
Dystonia	6 (1.2)	0	1 (0.6)
Headache	33 (6.5)	6 (4.1)	14 (8.8)
Parkinsonism	23 (4.5)	0	7 (4.4)
Somnolence	20 (4.0)	0	1 (0.6)
Cardiac disorders			
Tachycardia	8 (1.6)	1 (0.7)	1 (0.6)
Vascular disorders			
Orthostatic hypotension	2 (0.4)	0	0
Gastrointestinal disorders			
Nausea	11 (2.2)	0	2 (1.3)
Vomiting	9 (1.8)	0	0

Reproductive system and breast disorders			
Amenorrhea	6 (1.2)	0	1 (0.6)
Galactorrhea	4 (0.8)	0	0
General disorders and administration site conditions			
Injection site reaction	62 (12.3)	0	5 (3.1)

[a] During the open-label phase, subjects received several doses of the 1-month paliperidone palmitate injectable product followed by a single dose of INVEGA TRINZA prior to randomization to either placebo or INVEGA TRINZA in the subsequent double-blind phase (see *Pharmacodynamic Properties: Clinical efficacy*).
[b] The following terms were combined:
Tachycardia includes Tachycardia, Sinus tachycardia.
Injection site reaction includes Injection site reaction, Injection site erythema, Injection site extravasation, Injection site induration, Injection site inflammation, Injection site mass, Injection site nodule, Injection site pain, Injection site swelling.
Weight increased includes Weight increased, Waist circumference increased.
Upper respiratory tract infection includes Upper respiratory tract infection, Nasopharyngitis, Pharyngitis, Rhinitis.
Somnolence includes Somnolence, Sedation.
Akathisia includes Akisthisia, Restlessness.
Parkinsonism includes Parkinsonism, Cogwheel rigidity, Drooling, Extrapyramidal disorder, Hypokinesia, Muscle rigidity, Muscle tightness, Musculoskeletal stiffness, Salivary hypersecretion.
Dystonia includes Dystonia, Blepharospasm.
[c] Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

Treatment-Emergent Adverse Events in at Least 2% of Subjects in Either Treatment Group by MedDRA System Organ Class and Preferred Term During the Double-blind Phase (Study PSY-3011)

Body System Or Organ Class Dictionary-Derived Term	**INVEGA TRINZA (N=504) n (%)**	**1-month paliperidone palmitate injectable product (N=512) n (%)**
Total no. subjects with adverse events	342 (67.9)	340 (66.4)
Investigations	143 (28.4)	152 (29.7)
Weight increased	105 (20.8)	109 (21.3)
Weight decreased	14 (2.8)	14 (2.7)
Psychiatric disorders	89 (17.7)	85 (16.6)
Anxiety	27 (5.4)	24 (4.7)
Schizophrenia	18 (3.6)	14 (2.7)
Insomnia	16 (3.2)	24 (4.7)
Depression	11 (2.2)	6 (1.2)
Infections and infestations	82 (16.3)	81 (15.8)
Nasopharyngitis	36 (7.1)	33 (6.4)
Nervous system disorders	66 (13.1)	67 (13.1)
Akathisia	20 (4.0)	14 (2.7)
Headache	18 (3.6)	26 (5.1)
General disorders and administration site Conditions	51 (10.1)	35 (6.8)
Injection site induration	14 (2.8)	6 (1.2)
Injection site pain	12 (2.4)	14 (2.7)
Fatigue	10 (2.0)	5 (1.0)
Gastrointestinal disorders	49 (9.7)	40 (7.8)
Diarrhoea	10 (2.0)	6 (1.2)
Metabolism and nutrition disorders	22 (4.4)	22 (4.3)
Hyperglycaemia	4 (0.8)	10 (2.0)
Vascular disorders	18 (3.6)	12 (2.3)
Hypertension	12 (2.4)	7 (1.4)

Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Adverse events are coded using MedDRA version 17.1

Other clinical trial data

Paliperidone palmitate is hydrolyzed to paliperidone. Paliperidone is the active metabolite of risperidone, therefore, the adverse reaction profiles of these compounds (including both the oral and injectable formulations) are relevant to one another. This subsection includes additional adverse reactions reported with paliperidone and/or risperidone in clinical trials.

Additional adverse reactions reported in clinical trials of INVEGA TRINZA, not included in Table 5, are shown in Table 6a.

Table 6a. Additional Adverse Reactions Reported in Clinical Trials of INVEGA TRINZA

System/Organ Class
Adverse Reaction
Infections and infestations
Acarodermatitis, Bronchitis, Cellulitis, Cystitis, Ear infection, Eye infection, Influenza, Onychomycosis, Pneumonia, Respiratory tract infection, Sinusitis, Subcutaneous abscess, Tonsillitis
Blood and lymphatic system disorders
Anemia, Neutropenia, White blood cell count decreased
Immune system disorders
Hypersensitivity
Endocrine disorders
Glucose urine present, Hyperprolactinemia
Metabolism and nutritional disorders
Blood cholesterol increased, Blood triglycerides increased, Decreased appetite, Increased appetite, Polydipsia, Weight decreased[a]
Psychiatric disorders
Agitation, Anorgasmia, Blunted affect, Confusional state, Depression[a], Insomnia[a], Libido decreased, Nervousness, Nightmare, Sleep disorder
Nervous system disorders
Cerebral ischemia, Disturbance in attention, Dizziness, Dizziness postural, Dysarthria, Hypoesthesia, Paresthesia, Psychomotor hyperactivity, Syncope, Tardive dyskinesia, Tremor[a]
Eye disorders
Conjunctivitis, Dry eye, Glaucoma, Lacrimation increased, Vision blurred
Ear and labyrinth disorders
Ear pain, Tinnitus, Vertigo
Cardiac disorders
Atrioventricular block, Bradycardia, Conduction disorder, Electrocardiogram abnormal, Electrocardiogram QT prolonged, Palpitations, Postural orthostatic tachycardia syndrome
Vascular disorders
Hypertension[a], Hypotension
Respiratory, thoracic and mediastinal disorders
Cough, Dyspnea, Epistaxis, Nasal congestion, Pharyngolaryngeal pain, Respiratory tract congestion
Gastrointestinal disorders
Abdominal discomfort, Abdominal pain, Cheilitis, Constipation[a], Diarrhea[a], Dry mouth, Dyspepsia, Dysphagia, Flatulence, Gastroenteritis, Toothache[a]
Hepatobiliary disorders
Gamma-glutamyltransferase increased, Hepatic enzyme increased, Transaminases increased
Skin and subcutaneous tissue disorder
Acne, Drug eruption, Dry skin, Eczema, Erythema, Pruritus, Rash, Urticaria
Musculoskeletal and connective tissue disorders
Arthralgia, Back pain[a], Blood creatine phosphokinase increased, Joint stiffness, Joint swelling, Muscle spasms, Muscular weakness, Musculoskeletal pain[a], Neck pain
Renal and urinary disorders

Dysuria, Pollakiuria, Urinary incontinence

Reproductive system and breast disorders
Breast discomfort, Breast enlargement, Breast pain, Ejaculation disorder, Erectile dysfunction, Gynecomastia, Menstrual disorder[b], Sexual dysfunction

General disorders and administration site conditions
Asthenia, Body temperature increased, Chest discomfort, Chest pain, Chills, Drug withdrawal syndrome, Face edema, Fatigue[a], Gait abnormal, Malaise, Edema[b], Pyrexia

Injury, poisoning and procedural complications
Fall

[a] Reported by ≥2% of subjects treated with INVEGA TRINZA or 1-month paliperidone palmitate injectable product.
[b] **Edema includes:** generalized edema, edema peripheral, pitting edema. **Menstrual disorder includes:** menstruation irregular, oligomenorrhea.

Additional adverse reactions reported in other clinical trials of paliperidone and risperidone are shown in Table 6b.

Table 6b. Additional Adverse Reactions Reported in other Clinical Trials of Paliperidone and Risperidone.

System/Organ Class
Adverse Reaction
Blood and lymphatic system disorders
Eosinophil count increased
Immune system disorders
Anaphylactic reaction
Metabolism and nutritional disorders
Anorexia
Nervous system disorders
Balance disorder, Convulsion[a], Coordination abnormal, Depressed level of consciousness, Diabetic coma, Head titubation, Loss of consciousness, Neuroleptic malignant syndrome, Unresponsive to stimuli
Eye disorders
Eye movement disorder, Eye rolling, Ocular hyperemia, Photophobia
Cardiac disorders
Sinus arrhythmia
Vascular disorders
Flushing, Ischemia
Respiratory, thoracic and mediastinal disorders
Dysphonia, Hyperventilation, Pneumonia aspiration, Pulmonary congestion, Rales, Wheezing
Gastrointestinal disorders
Fecal incontinence, Fecaloma, Intestinal obstruction, Swollen tongue
Skin and subcutaneous tissue disorder
Dandruff, Hyperkeratosis, Seborrheic dermatitis, Skin discoloration
Musculoskeletal and connective tissue disorders
Posture abnormal, Rhabdomyolysis
Reproductive system and breast disorders
Breast engorgement, Vaginal discharge
General disorders and administration site conditions
Body temperature decreased, Induration, Thirst

[a] **Convulsion includes:** grand mal convulsion.

Events of particular interest to the class
Extrapyramidal symptoms (EPS). Data from the double-blind placebo-controlled phase of the long-term relapse prevention trial (see Pharmacodynamic Properties: Clinical efficacy) showed that the incidence of EPS-related AEs was higher in the

INVEGA TRINZA group (13 subjects [8.1%]) than in the placebo group (5 subjects [3.4%]). Evaluation of EPS included a pooled analysis of the following EPS groups: dyskinesia, dystonia, hyperkinesia, parkinsonism, and tremor.

Weight gain. In the double-blind placebo-controlled phase of the long-term relapse prevention trial, abnormal increases of ≥7% in body weight from double-blind baseline to double-blind end point were reported for 15 subjects (10%) in the INVEGA TRINZA group and 1 subject (1%) in the placebo group. Conversely, abnormal decreases in body weight (≥ 7%) from double-blind baseline to double blind end point were reported for 2 subjects (1%) in the INVEGA TRINZA group and 12 subjects (8%) in the placebo group. The mean changes in body weight from double-blind baseline to double-blind end point were +0.94 kg and 1.28 kg for the INVEGA TRINZA and placebo groups, respectively.

Laboratory tests: serum prolactin. During the double-blind placebo-controlled phase of the long-term relapse prevention trial, elevations of prolactin to above the reference range (> 13.13 ng/mL in males and > 26.72 ng/mL in females) were noted in a higher percentage of males and females in the INVEGA TRINZA group than in the placebo group (9% vs. 3% and 5% vs. 3%, respectively). In the INVEGA TRINZA group, the mean change from double-blind baseline to double blind end point was +2.90 ng/mL for males (vs. 10.26 ng/mL in the placebo group) and +7.48 ng/mL for females (vs. -32.93 ng/mL in the placebo group). One female (2.4%) in the INVEGA TRINZA group experienced an adverse reaction of amenorrhea, while no potentially prolactin-related adverse reactions were noted among females in the placebo group. There were no potentially prolactin-related adverse reactions among males in either group.

Postmarketing data

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during postmarketing experience with paliperidone and/or risperidone (Table 7). In the table, the frequencies are provided according to the following convention:

Very common ≥ 1/10
Common ≥ 1/100 and < 1/10
Uncommon ≥ 1/1000 and < 1/100
Rare ≥ 1/10000 and < 1/1000
Very rare < 1/10000, including isolated reports
Not known Cannot be estimated from the available data.

In Table 7, adverse reactions are presented by frequency category based on incidence in clinical trials, when known.

Table 7. Adverse Reactions Identified During Postmarketing Experience with Paliperidone and/or Risperidone by Frequency Category estimated from Clinical Trials with paliperidone injectable formulations

Blood and lymphatic system disorders	
Uncommon	Thrombocytopenia
Not known	Agranulocytosis
Endocrine disorders	
Rare	Inappropriate antidiuretic hormone secretion
Metabolism and nutrition disorders	
Uncommon	Diabetes mellitus[a]
Rare	Diabetic ketoacidosis, Hypoglycemia
Not known	Water intoxication
Psychiatric disorders	
Rare	Catatonia, Mania, Somnambulism
Not known	Sleep-related eating disorder
Nervous system disorders	
Uncommon	Dysgeusia
Eye disorders	
Not known	Floppy iris syndrome (intraoperative)
Cardiac disorders	
Rare	Atrial fibrillation
Vascular disorder	
Rare	Venous thrombosis
Not known	Pulmonary embolism
Respiratory, thoracic and mediastinal disorders	
Rare	Sleep apnea syndrome
Gastrointestinal disorders	
Rare	Pancreatitis
Not known	Ileus
Hepatobiliary disorders	
Not known	Jaundice
Skin and subcutaneous tissue disorders	
Uncommon	Alopecia
Not known	Angioedema, Stevens-Johnson syndrome/Toxic epidermal necrolysis
Renal and urinary disorders	
Rare	Urinary retention
Pregnancy, puerperium and perinatal conditions	
Not known	Drug withdrawal syndrome neonatal
Reproductive system and breast disorders	
Not known	Priapism
General disorders and administration site conditions	
Rare	Hypothermia, Injection site abscess, Injection site cellulitis, Injection site cyst, Injection site hematoma
Not known	Injection site necrosis, Injection site ulcer

[a] In placebo-controlled trials with the 1-month paliperidone palmitate injectable product, diabetes mellitus was reported in 0.32% in subjects treated with the 1-month injection compared to a rate of 0.39% in placebo group. During the double-blind, placebo-controlled phase of the long-term relapse-prevention trial with INVEGA TRINZA, diabetes mellitus was reported in 0.6% of INVEGA TRINZA -treated subjects compared to 0% in the placebo group. Overall incidence from all clinical trials was 0.63% in all subjects treated with paliperidone injectable formulations.

Very rarely, cases of anaphylactic reaction after administration of the 1-month paliperidone palmitate injectable product have been reported during postmarketing experience in patients who have previously tolerated oral risperidone or oral paliperidone.

INTERACTIONS

Caution is advised when prescribing INVEGA TRINZA with drugs known to prolong the QT interval.

Since paliperidone palmitate is hydrolyzed to paliperidone (see *Pharmacokinetic Properties*), results from studies with oral paliperidone should be taken into consideration when assessing drug-drug interaction potential.

Potential for INVEGA TRINZA to Affect Other Drugs

Paliperidone is not expected to cause clinically important pharmacokinetic interactions with drugs that are metabolized by cytochrome P-450 isozymes. *In vitro* studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of drugs metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6,

CYP2E1, CYP3A4, and CYP3A5. Therefore, paliperidone is not expected to inhibit clearance of drugs that are metabolized by these metabolic pathways in a clinically relevant manner. Paliperidone is also not expected to have enzyme inducing properties.

Paliperidone is a weak inhibitor of P-glycoprotein (P-gp) at high concentrations. No *in vivo* data are available and the clinical relevance is unknown.

Given the primary CNS effects of paliperidone (see *Adverse Reactions*), INVEGA TRINZA should be used with caution in combination with other centrally acting drugs and alcohol. Paliperidone may antagonize the effect of levodopa and other dopamine agonists.

Because of its potential for inducing orthostatic hypotension (see *Warnings and Precautions*: *Orthostatic Hypotension*), an additive effect may be observed when INVEGA TRINZA is administered with other therapeutic agents that have this potential.

Co-administration of oral paliperidone extended-release tablets at steady-state (12 mg once daily) with divalproex sodium extended-release tablets (500 mg to 2000 mg once daily) did not affect the steady-state pharmacokinetics of valproate.

Pharmacokinetic interaction between INVEGA TRINZA and lithium is unlikely.

Potential for Other Drugs to Affect INVEGA TRINZA
Paliperidone is not a substrate of CYP1A2, CYP2A6, CYP2C9, CYP2C19, and CYP3A5. This suggests that an interaction with inhibitors or inducers of these isozymes is unlikely. While *in vitro* studies indicate that CYP2D6 and CYP3A4 may be minimally involved in paliperidone metabolism, there are no indications *in vitro* nor *in vivo* that these isozymes play a significant role in the metabolism of paliperidone. *In vitro* studies have shown that paliperidone is a P-gp substrate.

Paliperidone is metabolized to a limited extent by CYP2D6 (see *Pharmacokinetic Properties: Metabolism and Elimination*). In an interaction study in healthy subjects in which oral paliperidone was administered concomitantly with paroxetine, a potent CYP2D6 inhibitor, no clinically relevant effects on the pharmacokinetics of paliperidone were observed.

Co-administration of oral paliperidone extended release once daily with carbamazepine 200 mg twice daily caused a decrease of approximately 37% in the mean steady-state C_{max} and AUC of paliperidone. This decrease is caused, to a substantial degree, by a 35% increase in renal clearance of paliperidone likely as a result of induction of renal P-gp by carbamazepine. A minor decrease in the amount of drug excreted unchanged in the urine suggests that there was little effect on the CYP metabolism or bioavailability of paliperidone during carbamazepine co-administration. On initiation of carbamazepine, the dose of INVEGA TRINZA should be re-evaluated and increased if necessary. Conversely, on discontinuation of carbamazepine, the dose of INVEGA TRINZA should be re-evaluated and decreased if necessary. Consideration should be given to the long-acting nature of INVEGA TRINZA.

Paliperidone, a cation under physiological pH, is primarily excreted unchanged by the kidneys, approximately half via filtration and half via active secretion. Concomitant administration of trimethoprim, a drug known to inhibit active renal cation drug transport, did not influence the pharmacokinetics of paliperidone.

Co-administration of a single dose of an oral paliperidone extended-release tablet 12 mg with divalproex sodium extended-release tablets (two 500 mg tablets once daily) resulted in an increase of approximately 50% in the C_{max} and AUC of paliperidone, likely the result of an increased oral absorption. Since no significant effect on the systemic clearance was observed, a clinically significant interaction would not be expected between divalproex sodium extended release tablets and INVEGA TRINZA intramuscular injection. This interaction has not been studied with INVEGA TRINZA.

Pharmacokinetic interaction between lithium and INVEGA TRINZA is unlikely.

Concomitant Use of INVEGA TRINZA with Risperidone or with oral paliperidone
Since paliperidone is the active metabolite of risperidone, caution should be exercised when INVEGA TRINZA is coadministered with risperidone or with oral paliperidone for extended periods of time. Safety data involving concomitant use of INVEGA TRINZA with other antispychotics is limited.

Concomitant use of INVEGA TRINZA with psychostimulants
The combined use of psychostimulants (e.g. methylphenidate) with paliperidone can lead to the emergence of extrapyramidal symptoms upon change of either or both treatments (see *Warnings and Precautions*).

Pregnancy and Breast-feeding
Pregnancy
The safety of intramuscularly-injected paliperidone palmitate or orally-dose paliperidone for use during human pregnancy has not been established.

A retrospective observational cohort study based on a US claims database compared the risk of congenital malformations for live births among women with and without antipsychotic use during the first trimester of pregnancy. Paliperidone, the active metabolite of risperidone, was not specifically evaluated in this study. The risk of congenital malformations with risperidone,

after adjusting for confounder variables available in the database, was elevated compared to no antipsychotic exposure (relative risk=1.26, 95% CI: 1.02-1.56). No biological mechanism has been identified to explain these findings and teratogenic effects have not been observed in non-clinical studies. Based on the findings of this single observational study, a causal relationship between *in utero* exposure to risperidone and congenital malformations has not been established.

No teratogenic effect was noted in any animal study. Laboratory animals treated with a high dose of oral paliperidone showed a slight increase in fetal deaths. Pregnancy parameters were not affected in rats given the intramuscular injection of the 1-month paliperidone palmitate injectable product. The high doses were toxic to the mothers. The offspring was not affected at oral exposures 20- to 22-fold the maximum human dose of oral paliperidone or at intramuscular exposures 6-fold the maximum human dose of the 1-month paliperidone palmitate injectable product.

Neonates exposed to antipsychotic drugs (including paliperidone) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms that may vary in severity following delivery. These symptoms in the neonates may include agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Since paliperidone has been detected in plasma up to 18 months after a single-dose administration of INVEGA TRINZA, consideration should be given to the long-acting nature of INVEGA TRINZA as neonates may be at risk from INVEGA TRINZA administration before pregnancy or during first and second trimesters as well.

INVEGA TRINZA should only be used during pregnancy if the benefits outweigh the risks. The effect of INVEGA TRINZA on labor and delivery in humans is unknown.

Breast-feeding
In animal studies with paliperidone and in human studies with risperidone, paliperidone was excreted in the milk. Therefore, women receiving INVEGA TRINZA should not breast-feed infants. Since paliperidone has been detected in plasma up to 18 months after a single-dose administration of INVEGA TRINZA, consideration should be given to the long-acting nature of INVEGA TRINZA as nursing infants may be at risk even from INVEGA TRINZA administration long before nursing.

Effects on Ability to Drive and Use Machines
INVEGA TRINZA may interfere with activities requiring mental alertness and may have visual effects (see Adverse Reactions). Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

OVERDOSE
Because INVEGA TRINZA is to be administered by health care professionals, the potential for overdosage by patients is low.

Symptoms and signs
In general, expected signs and symptoms are those resulting from an exaggeration of paliperidone's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, QT prolongation, and extrapyramidal symptoms. Torsade de pointes and ventricular fibrillation have been reported in the setting of overdose with oral paliperidone. In the case of acute overdosage, the possibility of multiple drug involvement should be considered.

Treatment
Consideration should be given to the extended-release *[prolonged-release]* nature of INVEGA TRINZA and the long apparent half-life of paliperidone when assessing treatment needs and recovery. There is no specific antidote to paliperidone. General supportive measures should be employed. Establish and maintain a clear airway and ensure adequate oxygenation and ventilation. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring for possible arrhythmias. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluid and/or sympathomimetic agents. In case of severe extrapyramidal symptoms, anticholinergic agents should be administered. Close supervision and monitoring should continue until the patient recovers.

PHARMACEUTICAL INFORMATION
List of Excipients
Inactive ingredients in INVEGA TRINZA are citric acid monohydrate, polyethylene glycol 4000, sodium dihydrogen phosphate monohydrate, sodium hydroxide, water for injection.

Incompatibilities
INVEGA TRINZA should not be mixed with any other product or diluent and is intended for intramuscular administration directly from the syringe in which it is packaged.

Shelf Life
2 years

Storage Conditions
Do not store above 30^0C. Keep out of the sight and reach of children

Nature and Contents of Container

Kit containing a syringe (cyclic-olefin-copolymer) prefilled with either 350 mg (1.75 ml), or 525 mg (2.625 ml) paliperidone (546 mg, or 819 mg paliperidone palmitate) suspension with a plunger stopper and tip cap (bromobutyl rubber), a backstop, and 2 types of commercially available needles: a thin wall 22G, 1½ inch safety needle and a thin wall 22G, 1-inch safety needle.

Instructions for Use and Handling and Disposal
INVEGA TRINZA
paliperidone palmitate
extended-release injectable suspension

Administer once every 3 months 

Shake syringe vigorously for at least 15 seconds 

For intramuscular injection only.
Do not administer by any other route.
Important

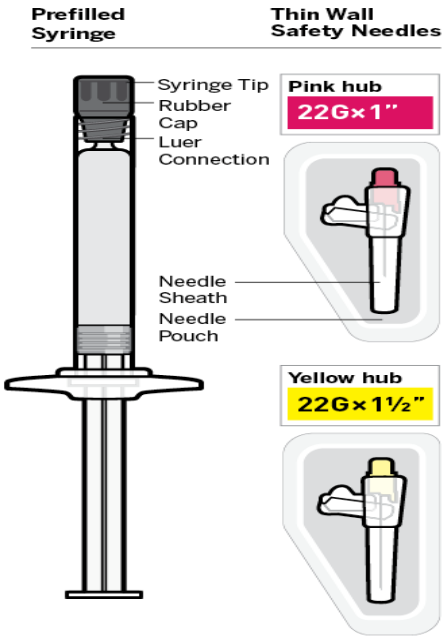
INVEGA TRINZA should be administered by a healthcare professional as a single injection. **Do not** divide dose into multiple injections.
INVEGA TRINZA is intended for intramuscular use only. Inject slowly, deep into the muscle taking care to avoid injection into a blood vessel.
Read complete instructions prior to use.

Dosing
This medication should be administered **once every 3 months**.

Preparation
Peel off tab label from the syringe and place in patient record.
INVEGA TRINZA requires **longer and more vigorous shaking** than the 1-month paliperidone palmitate injectable product. Shake the syringe vigorously, with the syringe tip pointing up, **for at least 15 seconds within 5 minutes prior to administration** (see Step 2).

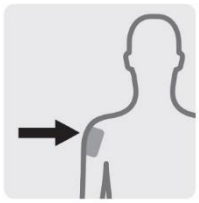
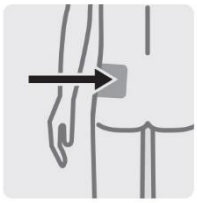
Thin Wall Safety
Needle Selection
Thin wall safety needles are designed to be used with INVEGA TRINZA. Therefore, it is important to **only use the needles provided in the** INVEGA TRINZA **kit**.

Dose pack contents



1. Select needle

Needle selection is determined by injection area and patient weight

If administering a Deltoid injection	If administering a Gluteal injection
	
If patient weighs: **Less than 90kg** pink hub 22G×1" **90kg or more** yellow hub 22G×1½"	**Regardless of patient weight**: yellow hub 22G×1½"

Immediately discard the unused needle in an approved sharps container. Do not save for future use.

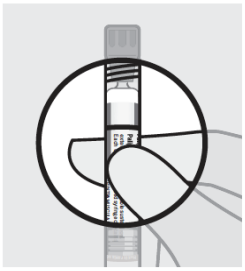
2. Prepare for injection

SHAKE VIGOROUSLY for at least 15 seconds

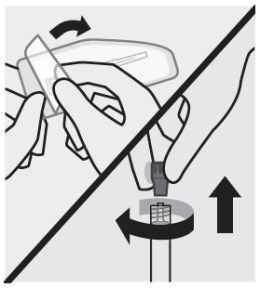
With the syringe tip pointing up, SHAKE VIGOROUSLY with a **loose wrist** for at least 15 seconds to ensure a homogeneous suspension.

NOTE: This medication requires longer and more vigorous shaking than the 1-month paliperidone palmitate injectable product.

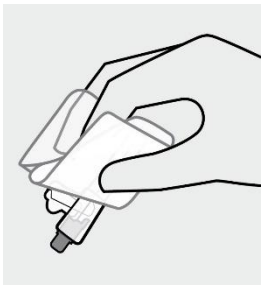
Proceed to the next step immediately after shaking. **If more than 5 minutes pass before injection, shake vigorously, with the syringe tip pointing up, again** for at least 15 seconds to re-suspend the medication.



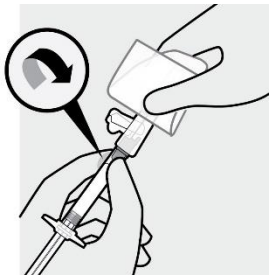
Check suspension
After shaking the syringe for 15 seconds, check the liquid in the viewing window. The suspension should appear uniform and milky white in color.
It is also normal to see small air bubbles.



Open needle pouch and remove cap
First, open needle pouch by peeling the cover back half way. Place on a clean surface. Then, holding the syringe upright, twist and pull the rubber cap to remove.

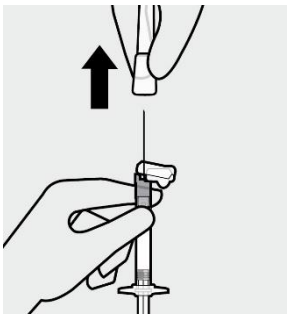


Grasp needle pouch
Fold back needle cover and plastic tray. Then, firmly grasp the needle sheath through the pouch, as shown.

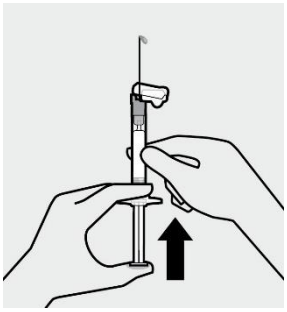


Attach needle

With your other hand, hold the syringe by the luer connection and attach it to the safety needle with a gentle clockwise twisting motion. **Do not** remove the pouch until the syringe and needle are securely attached.

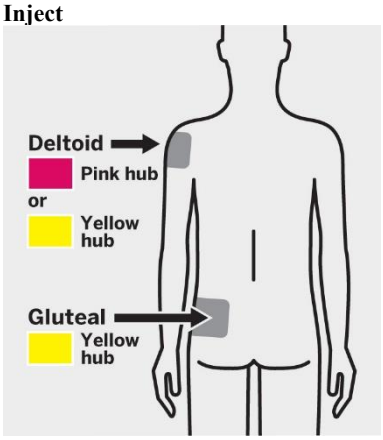


Remove needle sheath
Pull the needle sheath away from the needle in a straight motion. **Do not** twist the sheath, as this may loosen the needle from the syringe.



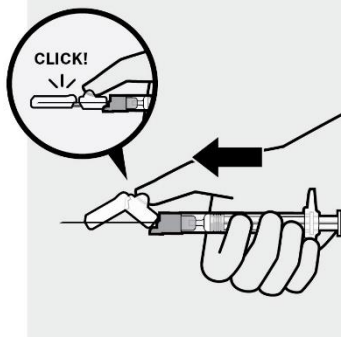
Remove air bubbles
Hold the syringe upright and tap gently to make any air bubbles rise to the top. Remove air by pressing the plunger rod upward carefully until a drop of liquid comes out of the needle tip.

3. Inject



Inject dose
Slowly inject the entire contents of the syringe intramuscularly, deep into the selected deltoid or gluteal muscle. **Do not administer by any other route.**

4. After injection



Secure needle
After the injection is complete, use your thumb or a flat surface to secure the needle in the safety device. The needle is secure when a "click" sound is heard.

Dispose properly
Dispose of the syringe and unused needle in an approved sharps container.

Thin wall safety needles are designed specifically for use with INVEGA TRINZA. Unused needle should be discarded and not saved for future use.

HOW SUPPLIED
- INVEGA TRINZA 350 mg Prolonged-Release Suspension for Intramuscular Injection
  Kit @ 1 prefilled syringe 350 mg (1.75 ml) paliperidone (as 546 mg paliperidone palmitate) suspension with a plunger rod and backstop + thin walled 22 gauge, 1 inch safety needle + thin walled 22 gauge, 1½ inch safety needle
  Reg. No.:

- INVEGA TRINZA 525 mg Prolonged-Release Suspension for Intramuscular Injection
  Kit @ 1 prefilled syringe 525 mg (2.625 ml) paliperidone (as 819 mg paliperidone palmitate) suspension with a plunger rod and backstop + thin walled 22 gauge, 1 inch safety needle + thin walled 22 gauge, 1½ inch safety needle
  Reg. No.:

HARUS DENGAN RESEP DOKTER

Manufactured by Janssen Pharmaceutica N.V., Beerse, Belgium
Registered by PT Integrated Healthcare Indonesia, Jakarta – Indonesia
Imported by PT Johnson & Johnson Indonesia, Jakarta – Indonesia
For adverse event and product quality complaint please contact drugsafety@jacid.jnj.com or Phone (021) 2935-3935

Based on CCDS 17Dec2017+07May2018+07Apr2020_IHI

INFORMASI PRODUK UNTUK PASIEN

INVEGA TRINZA
Paliperidone palmitate Injeksi Intramuskuler Pelepasan Lambat 3 Bulan

APA INFORMASI YANG PALING PENTING YANG HARUS DIKETAHUI TENTANG INVEGA TRINZA
INVEGA TRINZA dapat menyebabkan efek samping yang serius, termasuk: • Meningkatnya risiko kematian pada orang tua yang linglung, kehilangan ingatan dan telah kehilangan kesadaran akan realita (psikosis yang terkait dengan dementia). INVEGA TRINZA bukan untuk pengobatan psikosis yang terkait dengan dementia.

APA INVEGA TRINZA DAN APA KEGUNANNYA?
INVEGA TRINZA merupakan obat antipsikotik dan digunakan untuk mengobati skizofrenia pada pasien dewasa (18 tahun ke atas). INVEGA TRINZA digunakan setelah Anda sudah pernah mendapatkan pengobatan dengan injeksi 1 bulanan (INVEGA SUSTENA) selama 4 bulan. Setelah gejala yang Anda rasakan sudah berkurang atau hilang dari hasil pengobatan dengan injeksi 1 bulanan (INVEGA SUSTENA), INVEGA TRINZA digunakan untuk menjaga agar kondisi tetap terkendali, yakni mencegah kekambuhan. INVEGA TRINZA diberikan setiap 3 bulan sekali. INVEGA TRINZA tidak digunakan untuk mengobati skizofrenia pada pasien dibawah umur 18 tahun.
Skizofrenia adalah gangguan yang ditandai dengan gangguan halusinasi pendengaran, melihat atau merasakan hal-hal yang tidak sesuai dengan dunia nyata, keyakinan yang salah, kecurigaan yang tidak biasa, menarik diri, berbicara tidak teratur, dan berkurangnya respon dalam berperilaku dan emosional. Orang dengan gangguan ini juga dapat merasakan depresi, kecemasan, perasaan bersalah, dan ketegangan.
INVEGA TRINZA tidak boleh digunakan apabila Anda belum pernah mendapatkan pengobatan injeksi 1 bulanan (Invega Sustenna) selama 4 bulan.

KAPAN TIDAK MENGGUNAKAN INVEGA TRINZA
Jangan menggunakan INVEGA TRINZA jika Anda mengetahui bahwa Anda alergi (hipersensitif) terhadap Paliperidone atau kandungan lain dari INVEGA TRINZA, atau terhadap Risperidone yang merupakan obat antipsikotik lain yang menyerupai Paliperidone. Hipersensitivitas dapat dikenali dari ruam kulit, gatal-gatal, kesulitan bernafas atau bengkak pada wajah. Jika hal-hal ini terjadi, segera hubungi dokter Anda.

APA YANG PERLU SAYA KATAKANA KEPADA TENAGA KESEHATAN SEBELUM MENERIMA INVEGA TRINZA
INVEGA TRINZA belum diteliti pada pasien lanjut usia dengan demensia. Namun, pasien lanjut usia dengan demensia, yang diberikan pengobatan dengan tipe obat yang sama dapat meningkatkan resiko stroke atau kematian.
Jika Anda mempunyai kondisi-kondisi berikut, beritahukan kepada dokter Anda agar dokter Anda dapat menyesuaikan dosis dan memantau Anda untuk beberapa waktu.
- jika Anda memiliki penyakit Parkinson atau Demensia.
- jika Anda pernah di diagnosa dengan suatu kondisi dimana gejalanya meliputi suhu tubuh yang tinggi dan kekakuan otot (juga dikenal sebagai *Neuroleptic Malignant Syndrome*).
- jika Anda pernah mengalami gerakan abnormal dari lidah atau wajah (*Tardive Dyskinesia*).
- jika Anda beresiko diabetes atau kadar gula darah tinggi.
- jika Anda memiliki penyakit jantung atau pengobatan terhadap penyakit jantung yang membuat Anda rentan terhadap tekanan darah rendah, atau rentan terhadap penurunan tekanan darah atau merasa pusing ketika Anda berdiri dari posisi berbaring atau dari posisi duduk.
- jika Anda memiliki penyakit epilepsi.
- jika Anda memiliki atau pernah memiliki jumlah sel darah putih yang rendah. Segera beritahukan dokter Anda jika Anda mengalami demam atau infeksi saat diberikan INVEGA TRINZA.
- jika Anda mengalami kerusakan fungsi ginjal. Dokter Anda dapat mengurangi dosis INVEGA TRINZA jika fungsi ginjal ada menurun.
- jika Anda kehilangan fungsi hati.
- jika Anda memiliki gangguan ereksi.

- jika Anda memiliki masalah dengan pengaturan suhu tubuh.
- jika Anda atau orang lain dalam keluarga Anda memiliki riwayat dalam pembekuan darah.
  Pembekuan darah di paru-paru dan kaki pernah terlihat pada pasien yang menggunakan obat yang sama dengan INVEGA TRINZA. Pembekuan darah di paru-paru dapat berakibat fatal.
- masalah jantung, termasuk serangan jantung, gagal jantung, ritme jantung yang abnormal, dan gejala QT yang panjang.

Bahkan untuk pasien yang sebelumnya dapat mentoleransi Paliperidone atau Risperidone oral, reaksi alergi dilaporkan sangat jarang setelah menggunakan produk Paliperidone palmitat injeksi 1 bulan dan ada kemungkinan bahwa reaksi alergi bisa terjadi dengan INVEGA TRINZA. Segera dapatkan bantuan medis jika Anda mengalami ruam, pembengkakan tenggorokan, gatal-gatal, atau masalah pernapasan yang mungkin tanda-tanda dari reaksi alergi yang serius.

Kenaikan berat badan telah terlihat pada pasien yang menerima obat-obatan antipsikotik. Dokter Anda mungkin akan memantau berat badan Anda saat Anda sedang menggunakan INVEGA TRINZA.

Selama operasi pada mata untuk kekeruhan lensa (katarak), pupil (lingkaran hitam di tengah mata Anda) mungkin tidak bertambah besar sesuai kebutuhan. Demikian juga, iris (bagian berwarna dari mata) dapat menjadi terkulai selama operasi dan dapat menyebabkan kerusakan mata. Jika Anda berencana untuk memiliki operasi pada mata Anda, pastikan Anda memberitahu dokter mata Anda bahwa Anda sedang menggunakan obat ini.

Kehamilan

Katakan kepada dokter jika Anda sedang hamil, berpikir kemungkinan sedang hamil, atau berencana untuk hamil. Anda tidak boleh menggunakan INVEGA TRINZA selama kehamilan kecuali hal ini telah dibicarakan dengan dokter Anda. Gemetar, kekakuan otot dan/atau kelemahan, mengantuk, agitasi, masalah pernapasan, atau kesulitan dalam menyusui dapat terjadi pada bayi Anda jika Anda menggunakan INVEGA TRINZA selama kehamilan Anda, dan bahkan jika Anda menggunakan INVEGA TRINZA sebelum hamil.

Menyusui

Jangan menyusui saat Anda sedang menggunakan INVEGA TRINZA. INVEGA TRINZA dapat masuk ke dalam kelenjar susu. Konsultasikan dengan dokter Anda dalam hal ini.

Mengemudi atau mengoperasikan mesin

INVEGA TRINZA dapat mempengaruhi kewaspadaan Anda dan dapat mempengaruhi penglihatan Anda. Oleh karena itu, Anda disarankan untuk tidak mengemudi atau mengoperasikan mesin sebelum Anda tahu seberapa sensitif Anda terhadap INVEGA TRINZA.

Obat-obatan lain dan alkohol

Beritahu dokter atau apoteker Anda jika Anda menggunaan atau baru saja menggunakan obat lain, termasuk obat-obatan yang diperoleh tanpa resep dokter. Perhatikan bahwa beberapa obat-obatan dapat meningkatkan kadar Paliperidone dalam darah Anda, yang dapat menghasilkan peningkatan efek samping menyerupai overdosis INVEGA TRINZA. (Lihat bagian overdosis di bawah.)
INVEGA TRINZA dapat membuat Anda mengantuk, berhati-hatilah jika menggunakan INVEGA TRINZA bersamaan dengan obat-obatan lain yang juga dapat menyebabkan mengantuk.
INVEGA TRINZA dapat menurunkan tekanan darah, berhati-hatilah jika menggunakan INVEGA TRINZA bersamaan dengan obat-obatan lain yang juga dapat menurunkan tekanan darah.
INVEGA TRINZA dapat mengurangi efek dari obat untuk penyakit Parkinson dan *restless legs syndrome* (misalnya, levodopa).

INVEGA TRINZA harus digunakan dengan hati-hati dengan obat-obatan yang meningkatkan aktivitas sistem saraf pusat (psikostimulan seperti methylphenidate).
Konsumsi alkohol harus dihindari ketika menggunakan INVEGA TRINZA.

BAGAIMANA CARA MENGGUNAKAN INVEGA TRINZA DAN BERAPA BANYAK

INVEGA TRINZA digunakan setelah Anda mendapatkan pengobatan dengan injeksi 1 bulanan (INVEGA SUSTENA) selama 4 bulan. Seperti injeksi 1 bulanan, INVEGA TRINZA diberikan oleh dokter atau tenaga kesehatan profesional lainnya di rumah sakit atau klinik. Dokter Anda akan memberitahu Anda kapan Anda harus datang ke rumah sakit atau klinik untuk penyuntikan. Hal ini penting untuk tidak melewatkan dosis yang sudah dijadwalkan. Jika Anda tidak dapat memenuhi janji dengan dokter, pastikan Anda menghubungi dokter Anda segera sehingga janji lain dapat dibuat sesegera mungkin. Dokter Anda mungkin juga ingin bertemu Anda bahkan jika Anda tidak dijadwalkan untuk penyuntikan INVEGA TRINZA.
INVEGA TRINZA diberikan melalui suntikan ke dalam otot lengan atas atau pantat setiap 3 bulan sekali. Tergantung pada gejala Anda, dokter Anda dapat meningkatkan atau mengurangi jumlah obat yang Anda terima pada saat injeksi yang dijadwalkan.

Jika Anda menerima dosis INVEGA TRINZA lebih besar dari yang seharusnya
Obat ini akan diberikan kepada Anda di bawah pengawasan medis; oleh karena itu, kemungkinannya sangat kecil Anda akan diberikan terlalu banyak.
Pasien yang telah diberikan terlalu banyak Paliperidone mungkin mengalami gejala berikut: mengantuk, denyut jantung cepat, tekanan darah rendah, elektrokardiogram abnormal, atau gerakan lambat atau abnormal wajah, tubuh, lengan, atau kaki.

Jika Anda menghentikan INVEGA TRINZA
Anda akan kehilangan efek obat tersebut. Anda tidak dapat menghentikan obat ini kecuali atas perintah dokter karena gejala-gejala lama Anda dapat kembali.
Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan produk ini, tanyakan kepada dokter atau apoteker Anda.

Anak-anak dan remaja
INVEGA TRINZA tidak digunakan untuk mengobati skizofrenia pada pasien dibawah umur 18 tahun.

Pasien dengan gangguan ginjal dan hati
Dokter dapat menyesuaikan dosis INVEGA TRINZA berdasarkan fungsi ginjal Anda. INVEGA TRINZA belum diteliti pada pasien dengan gangguan hati, tetapi berdasarkan pengalaman dengan Paliperidone oral, penyesuaian dosis biasanya tidak diperlukan pada pasien dengan gangguan hati ringan sampai sedang. Dokter akan menggunakan penilaian terbaiknya apakah INVEGA TRINZA dapat dipertimbangkan untuk digunakan pada pasien dengan gangguan hati yang berat.

EFEK YANG TIDAK DIINGINKAN

Seperti semua obat-obatan, INVEGA TRINZA dapat menyebabkan efek samping, meskipun tidak semua orang mengalaminya.
Jarang, reaksi alergi parah yang ditandai dengan demam, bengkak pada mulut, wajah, bibir atau lidah, sesak napas, gatal-gatal, ruam kulit dan kadang-kadang penurunan tekanan darah (seperti 'reaksi anafilaksis') dapat terjadi. Jika ini terjadi, segera dapatkan bantuan medis.
Bahkan jika Anda sebelumnya toleransi terhadap Risperidone atau Paliperidone oral, reaksi alergi yang sangat jarang dapat terjadi setelah menerima suntikan INVEGA TRINZA. Segera dapatkan bantuan medis jika Anda mengalami ruam, pembengkakan tenggorokan, gatal-gatal, atau masalah pernapasan yang mungkin ini adalah tanda-tanda dari reaksi alergi yang serius.
Pada pasien usia lanjut dengan demensia, obat-obatan di kelompok yang sama seperti INVEGA TRINZA telah dikaitkan dengan efek samping termasuk kelemahan mendadak atau mati rasa pada wajah, lengan, atau kaki, bicara cadel, atau penglihatan kabur. Gejala-gejala ini mungkin berhubungan dengan stroke. Jika salah satu terjadi, bahkan

untuk waktu singkat, segera dapatkan bantuan medis. Jika salah satu dari efek samping semakin serius, atau jika Anda melihat efek samping apapun tidak tercantum dalam selebaran ini, beritahu dokter atau apoteker.

Efek samping yang sangat umum: dapat mempengaruhi pada lebih dari 1 dari 10 orang
- Kesulitan tidur atau tidak bisa tidur

Efek samping yang umum: dapat mempengaruhi hingga 1 dari 10 orang
- Gejala batuk umum, infeksi saluran kemih, merasa seperti akan mengalami flu.
- Gula darah tinggi, peningkatan berat badan, penurunan berat badan.
- Lekas marah, depresi, kecemasan.
- Gejala Parkinson: pegerakan lambat, dengan tremor, kekakuan dan berjalan menyeret, gelisah.
- Tremor (gemetar).
- *Dystonia*: kontraksi involunter lambat atau berkelanjutan otot. Sementara itu dapat melibatkan setiap bagian dari tubuh (dan dapat mengakibatkan postur abnormal), dystonia sering melibatkan otot-otot wajah, termasuk gerakan abnormal mata, mulut, lidah atau rahang.
- *Dyskinesia*: gerakan otot tak sadar dan dapat berulang, spastik atau gerakan menggeliat, atau kedutan.
- Pusing, mengantuk atau kurang waspada, sakit kepala.
- Detak jantung menjadi lambat, detak jantung menjadi cepat.
- Tekanan darah tinggi.
- Batuk, hidung tersumbat.
- Sakit perut, muntah, mual, sembelit, diare, gangguan pencernaan, sakit gigi.
- Peningkatan transaminase hati dalam darah.
- Ruam.
- Nyeri tulang atau otot, sakit punggung, nyeri sendi.
- Kehilangan periode menstruasi.
- Demam, menjadi lemah, kelelahan.
- Reaksi di tempat suntikan, termasuk gatal-gatal, nyeri atau bengkak.

Efek samping yang tidak umum: dapat mempengaruhi hingga 1 dalam 100 orang
- Pneumonia, bronkitis, infeksi saluran pernapasan, infeksi sinus, infeksi kandung kemih, infeksi telinga, radang amandel, infeksi jamur pada kuku, infeksi kulit.
- Jumlah sel darah putih menurun, penurunan trombosit (sel darah yang membantu menghentikan pendarahan).
- Anemia.
- Reaksi alergi.
- INVEGA TRINZA dapat meningkatkan kadar hormon yang disebut "prolaktin" pada tes darah (bisa atau tidak bisa menimbulkan gejala). Ketika gejala prolaktin tinggi dapat terjadi: (pada pria) pembesaran payudara, kesulitan dalam mendapatkan atau mempertahankan ereksi, atau disfungsi seksual lainnya; (pada wanita) ketidaknyamanan payudara, keluar susu dari payudara, kehilangan siklus menstruasi, atau masalah lain dengan siklus Anda.
- Diabetes atau memburuknya diabetes, peningkatan insulin (hormon yang mengontrol kadar gula darah) dalam darah Anda, poeningkatkan nafsu makan, kehilangan nafsu makan sehingga kekurangan gizi dan berat badan rendah, penurunan nafsu makan, trigliserida darah tinggi (lemak), peningkatan kolesterol dalam Anda darah.
- Gangguan tidur, penurunan dorongan seksual, gugup, bermimpi buruk.
- *Tardive dyskinesia* (berkedut atau gerakan menyentak yang tidak dapat dikontrol pada wajah Anda, lidah, atau bagian lain dari tubuh Anda).
- Pingsan, dorongan untuk menggerakkan bagian-bagian tubuh Anda, pusing setelah berdiri, susah berkonsentrasi, gangguan berbicara, kehilangan pengecap rasa atau abnormal pengecap rasa, mengurangi sensasi kulit untuk rasa sakit dan sentuhan, kesemutan, menusuk, atau mati rasa kulit.
- Pandangan kabur, infeksi mata atau "mata merah", mata kering.
- Sensasi berputar (vertigo), bunyi di telinga, sakit telinga.
- Gangguan dalam konduksi antara bagian atas dan bawah dari jantung, konduksi listrik abnormal jantung, perpanjangan interval QT dari hati Anda, detak jantung cepat saat berdiri, abnormal elektrokardiogram (EKG), dada berdebar (palpitasi).

- Tekanan darah rendah, tekanan darah rendah pada berdiri (akibatnya, beberapa orang setelah menggunakan INVEGA TRINZA dapat merasa lemas, pusing, atau mungkin pingsan ketika mereka berdiri atau duduk tiba-tiba).
- Sesak napas, sakit tenggorokan, mimisan.
- Ketidaknyamanan perut, infeksi pada perut atau usus, mulut kering, gas atau angin berlebihan.
- Peningkatan GGT (enzim hati yang disebut *gamma glutamyltransferase*) dalam darah Anda, meningkatkan enzim hati dalam darah Anda.
- Gatal-gatal (atau "*nettle rash*"), gatal, rambut rontok, eksim, kulit kering, kulit kemerahan, jerawat. Peningkatan CPK (*creatine phosphokinase*) dalam darah Anda, sebuah enzim yang saat kerusakan otot, kejang otot, kekakuan sendi, kelemahan otot, nyeri leher.
- Inkontinensia (kurangnya kontrol) urin, sering membuang urin, nyeri saat membuang urin.
- Kesulitan mendapatkan dan menjaga ereksi (disfungsi ereksi), gangguan ejakulasi, kehilangan siklus menstruasi atau masalah lain dengan siklus wanita, pembesaran payudara pada pria, keluar air susu dari payudara, disfungsi seksual, nyeri pada payudara.
- Pembengkakan pada wajah, mulut, mata, atau bibir, pembengkakan tubuh, lengan, atau kaki, perubahan dalam cara Anda berjalan, nyeri dada, rasa tidak nyaman di dada, merasa tidak enak badan, penebalan kulit.
- Jatuh.

Efek samping yang jarang: dapat mempengaruhi hingga 1 dari 1000 orang
- Infeksi mata, kudis, abses di bawah kulit.
- Penurunan jenis sel darah putih yang membantu melindungi Anda terhadap infeksi, peningkatan eosinofil (sejenis sel darah putih) dalam darah Anda.
- Sekresi yang tidak biasa dari hormon yang mengontrol volume urine, gula dalam urin.
- Komplikasi yang membahayakan dari diabetes yang tidak terkontrol, gula darah rendah, meminum air berlebihan.
- Suasana hati yang meningkat (mania), kebingungan, kurangnya emosi, ketidakmampuan untuk mencapai orgasme, tidak bergerak atau tidak memberikan respon saat terjaga (katatonia), tidur sambil berjalan.
- Sindrom neuroleptik malignan (kebingungan, berkurangnya atau hilangnya kesadaran, demam tinggi, dan kekakuan otot yang parah).
- Gangguan pada pembuluh darah di otak termasuk tiba-tiba kehilangan suplai darah ke otak (stroke atau "mini" stroke), tidak responsif terhadap rangsangan, hilangnya kesadaran, rendahnya tingkat kesadaran, kejang, gangguan keseimbangan.
- Glaukoma (peningkatan tekanan dalam bola mata), masalah dengan gerakan mata, mata bergulir.
- Penglihatan terlalu peka terhadap cahaya, peningkatan produksi air mata, mata menjadi merah.
- Fibrilasi atrium (irama jantung yang abnormal), detak jantung tidak teratur.
- Bekuan darah di kaki, kemerahan.
- Kesulitan bernapas saat tidur (*sleep apnea*), sumbatan pada paru, sumbatan pada saluran pernapasan.
- Mengi.
- Radang pankreas, pembengkakan pada lidah, feses menjadi lembek, feses menjadi keras, kesulitan menelan, bibir pecah-pecah.
- Ruam pada kulit yang berkaitan dengan obat, penebalan kulit, ketombe.
- Pembengkakan sendi.
- Ketidakmampuan untuk mengeluarkan urin.
- Rasa tidak nyaman pada payudara, pembesaran kelenjar di payudara Anda, pembesaran payudara, keputihan.
- Suhu tubuh sangat rendah, kedinginan, peningkatan suhu tubuh, merasa haus, gejala putus obat, akumulasi nanah yang disebabkan oleh infeksi di tempat suntikan, infeksi kulit mendalam, kista di tempat suntikan, memar di tempat suntikan.

Tidak diketahui: frekuensi tidak dapat diperkirakan dari data yang tersedia
- Penurunan jumlah sel darah putih tertentu yang diperlukan untuk melawan infeksi dalam tubuh yang dapat membahayakan.
- Reaksi alergi berat yang ditandai dengan demam, bengkak pada mulut, wajah, bibir atau lidah, sesak napas, gatal-gatal, ruam kulit dan kadang-kadang penurunan tekanan darah.
- Asupan air yang berlebihan.

- Gangguan pola makan dimana seseorang dapat mengkonsumsi makanan pada saat tidur.
- Koma karena diabetes yang tidak terkontrol, koordinasi abnormal, kepala gemetar.
- Sindrom *floppy iris* (selama operasi pada mata untuk kekeruhan lensa [katarak], iris [bagian berwarna dari mata] dapat menjadi terkulai selama operasi dan dapat menyebabkan kerusakan mata. Jika Anda berencana untuk operasi pada mata Anda, pastikan Anda memberitahu dokter mata Anda bahwa Anda menggunakan obat ini).
- Gumpalan darah di paru-paru, penurunan oksigen di bagian tubuh Anda (karena penurunan aliran darah).
- Pernapasan menjadi cepat dan pendek, pneumonia disebabkan oleh tersedak makanan, suara paru-paru yang gemercik, gangguan suara.
- Sumbatan pada usus, berkurangnya gerakan usus yang dapat menyebabkan penyumbatan.
- Menguningnya kulit dan mata (jaundice).
- Reaksi alergi yang serius yang disertai dengan pembengkakan yang mungkin melibatkan tenggorokan dan menyebabkan kesulitan bernapas, perubahan warna kulit, kulit kepala kering dan gatal.
- Ruam yang parah atau mengancam jiwa disertai dengan kulit melepuh dan mengelupas yang mungkin mulai terjadi di dalam dan disekitar mulut, hidung, mata dan alat kelamin dan menyebar ke area lain pada tubuh (*Stevens-Johnson syndrome* atau nekrolisis epidermal toksik).
- Gangguan serat otot dan nyeri pada otot (*rhabdomyolysis*), postur abnormal.
- Bayi baru lahir dari ibu yang menggunakan INVEGA TRINZA selama kehamilan mungkin mengalami efek samping dari gejala obat dan / atau penghentian, seperti mudah marah, lambat, atau kontraksi otot berkelanjutan, gemetar, kantuk, bernafas, atau masalah makan.
- *Priapism* (penis ereksi berkepanjangan yang mungkin memerlukan pengobatan bedah).
- Penurunan suhu tubuh, sel-sel kulit mati di tempat suntikan, luka di tempat suntikan.

OVERDOSIS

Karena INVEGA TRINZA disimpan dan diberikan oleh tenaga medis profesional, kemungkinan overdosis untuk pasien rendah.
Dalam kejadian overdosis, satu atau lebih dari tanda-tanda berikut mungkin terjadi: kesadaran berkurang, mengantuk, gemetar berlebihan, kekakuan otot berlebihan, jantung berdetak cepat, dan tekanan darah rendah. Kasus konduksi normal listrik di jantung (perpanjangan QT) dan kejang telah dilaporkan. Overdosis dapat terjadi jika Anda menggunakan obat lain bersama-sama dengan INVEGA TRINZA. Jika Anda mengalami gejala di atas hubungi dokter Anda sehingga Anda dapat diobati jika menerima terlalu banyak INVEGA TRINZA.

Informasi untuk Dokter pada kasus overdosis
- Membuat dan mempertahankan jalan nafas yang jika pasien telah kehilangan kesadaran.
- Suntikkan simpatomimetik jika tekanan darah rendah.
- Pemantauan EKG diperlukan: dipindahkan di rumah sakit.
- Pertimbangkan sifat pelepasan lambat INVEGA TRINZA.

CARA MENYIMPAN INVEGA TRINZA

Jauhkan dari jangkauan dan penglihatan anak-anak.
Jangan menggunakan INVEGA TRINZA setelah tanggal kadaluwarsa yang tertera pada dus. Tanggal kadaluwarsa mengacu pada hari terakhir dari bulan itu.
Simpanlah INVEGA TRINZA sesuai dengan kondisi penyimpanan yang tertulis pada dus.
Obat tidak boleh tidak dibuang melalui air limbah atau sampah rumah tangga. Tanyakan Apoteker Anda bagaimana cara untuk membuang obat-obatan yang tidak lagi diperlukan. Langkah-langkah ini akan membantu untuk melindungi lingkungan.

APAKAH KANDUNGAN INVEGA TRINZA?

Zat aktif yang terkandung dalam INVEGA TRINZA adalah paliperidone (sebagai paliperidone palmitat). INVEGA TRINZA berupa cairan suspensi berwarna putih sampai putih pucat di dalam jarum suntik untuk digunakan secara suntikan intramuskular dalam beberapa kekuatan di bawah ini:

546 mg paliperidone palmitat setara dengan 350 mg paliperidone
819 mg paliperidone palmitat setara dengan 525 mg paliperidone
Bahan lainnya adalah: asam sitrat monohydrate, polietilen glikol 4000, polisorbat 20, natrium dihidrogen fosfat monohidrat, natrium hidroksida, air untuk injeksi.

Yang Harus Anda Ketahui Tentang Obat
Selalu beritahukan Dokter atau Apoteker Anda jika Anda menggunakan obat-obatan lain karena beberapa obat tidak boleh digunakan secara bersamaan.
Obat-obatan diteliti dengan baik sebelum diberikan kepada pasien. Oleh karena itu, jika obat ini tidak digunakan secara tepat dapat menimbulkan kesalahan. Gunakan obat sebagai berikut:
- hanya untuk tujuan pengobatan;
- hanya dalam jumlah/dosis yang disarankan;
- hanya untuk periode yang direkomendasikan.

Jauhkan semua obat-obatan dari jangkauan anak-anak.
Jangan pernah membiarkan orang lain untuk menggunakan obat-obatan yang direkomendasikan untuk Anda dan jangan menggunakan obat yang diresepkan untuk orang lain.
Simpan semua obat dalam kemasan aslinya dan di tempat yang kering (tidak boleh di kamar mandi, misalnya!).
Biasakan untuk mengembalikan obat-obatan yang tidak terpakai atau yang sudah lama kepada Apoteker Anda.
Jika seseorang telah mengalami overdosis obat, segera hubungi dokter.

HARUS DENGAN RESEP DOKTER

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Untuk pelaporan efek yang tidak diinginkan dan keluhan produk silahkan menghubungi drugsafety@jacid.jnj.com atau telepon (021) 2935-3935

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